REMARKS

Reconsideration of the application is respectfully requested.

The claims under consideration are Claims 1-43.

Pursuant to the restriction requirement having been made final, only Claims 28-37 have been examined.

Reconsideration of the rejection of Claim 32 under 35 U.S.C. §112, second paragraph, for insufficient antecedent basis in Claim 29 is respectfully requested.

Claim 32 is dependent from Claim 29. Step (c) of Claim 29 involves the reaction of an amine of formula (XA) with reactive functional derivatives of acids of the formula (XIII). Claim 32 lists particular acids in form of reactive functional derivatives which are within the scope of Claim 29 and such is therefore properly dependent therefrom. Support for the proper dependency appears, e.g., on Page 20 below formula (XIII) and on Page 22, first paragraph.

For example, ethyl oxalyl chloride (listed in Claim 32) having the formula

$$CH_3CH_2O\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-Cl$$
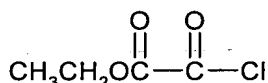
is a reactive functional derivative of the carboxylic acid of the formula

$$CH_3CH_2O\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}OH$$
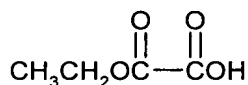
which is a compound of formula (XIII), wherein R_1 is alkoxy (ethoxy) and n is zero; ethyl oxalyl chloride reacts with an amine of formula (XA) in step (c) of Claim 29 to form an amide of formula (XIB), in which R_1 is ethoxy and n is zero.

Ethyl oxalyl chloride, contrary to the Examiner's assertion, is <u>not</u> a salt of a carboxylic acid, but is an acyl (acid) chloride.

Enclosed herewith as "Attachment A" is an excerpt from a standard textbook in Organic Chemistry from which it can be seen that an acyl chloride (as is, e.g., ethyl oxalyl chloride) is a reactive chloro derivative of the corresponding carboxylic acid (the –OH grouping in –COOH being replaced by –Cl), which reacts with amines to form amides, the reaction involved in step (c) of Claim 29.

In view of the above, it is respectfully submitted that no issue of improper dependency of Claim 32 is involved and that the rejection of Claim 32 under 35 U.S.C. §112 should be withdrawn.

As to the provisional rejection of Claims 28-37 for obviousness double-patenting over co-pending Application No. 09/931,683, the Applicant promises to file a terminal disclaimer when all claims are otherwise allowable, and if such is required by the status of the co-pending application.

Reconsideration of the provisional rejection of Claims 36 and 37 for obviousness double-patenting over Claims 9 and 24 of co-pending Application No. 09/533, 219 is also respectfully requested.
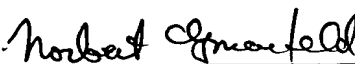
Claim 9 of Application No. 09/533,219 is directed to a compound and Claim 24 is a method-of-use claim for such a compound.

Claims 36 and 37 are clearly only directed to a process of making the compounds.

Therefore, it is respectfully submitted that no issue of obviousness double-patenting is involved and that the rejection of Claims 36 and 37 for obviousness double-patenting over Application No. 09/533,219 should be withdrawn.

Respectfully submitted,

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NG/ld

Encl.: Attachment A

Date: September 23, 2003

Chemistry of
Organic Compounds

CARL R. NOLLER

Professor of Chemistry, Stanford University

SECOND EDITION
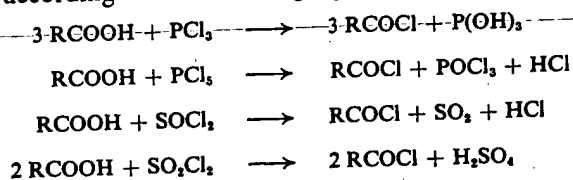
W. B. SAUNDERS COMPANY

Philadelphia   1957   London

The **higher normal acids** having an even number of carbon atoms are obtained by the hydrolysis of fats (p. 183). A few branched-chain fatty acids have been isolated from microorganisms. Hydrolysis of the antibiotic from *Bacillus polymyxa* gives 6-methyloctanoic acid. **Tuberculostearic acid,** from the fatty capsule of the tuberculosis bacillus, *Mycobacterium tuberculosis*, is 10-methyl-stearic acid. In Germany during World War II, paraffin from the Fischer-Tropsch synthesis (p. 83) was oxidized by air at 115°–125° in the presence of manganese salts to give a complex mixture of higher acids which served as a substitute for acids derived from natural fats.

ACYL HALIDES

Preparation

Since acyl halides result from the replacement of the hydroxyl group by a halogen atom, their structure is represented by the general formula $R-\overset{\overset{\displaystyle O}{\|}}{C}-X$. An inorganic acid halide such as phosphorus trichloride, phosphorus penta-chloride, thionyl chloride, or sulfuryl chloride must be used to effect this replacement. These compounds are the acid chlorides of phosphorous, phos-phoric, sulfurous, and sulfuric acids, respectively. Their reactions with organic acids take place according to the following equations.

$$3\,RCOOH + PCl_3 \longrightarrow 3\,RCOCl + P(OH)_3$$

$$RCOOH + PCl_5 \longrightarrow RCOCl + POCl_3 + HCl$$

$$RCOOH + SOCl_2 \longrightarrow RCOCl + SO_2 + HCl$$

$$2\,RCOOH + SO_2Cl_2 \longrightarrow 2\,RCOCl + H_2SO_4$$

If the sodium salt of the organic acid is used, phosphorus oxychloride also will react.

$$2\,RCOONa + POCl_3 \longrightarrow 2\,RCOCl + NaCl + NaPO_3$$
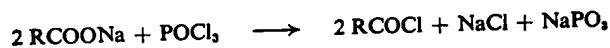
Hence when the sodium salt reacts with phosphorus pentachloride, three fifths of the total chlorine is available instead of only one fifth.

$$3\,RCOONa + PCl_5 \longrightarrow 3\,RCOCl + 2\,NaCl + NaPO_3$$
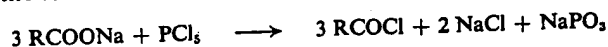
Thionyl chloride, $SOCl_2$, has an advantage over other reagents in that the acyl chloride is obtained in good yield and can be purified readily, the other products of the reaction being gases. For these reasons thionyl chloride is used for small scale preparations even though it is somewhat more expensive than the other reagents.

The **acyl bromides** may be made from organic acids and inorganic acid bromides analogous to the preparation of acyl chlorides. **Acyl iodides** are made ordinarily from the acyl chloride and calcium iodide or dry hydrogen iodide.

$$2\,RCOCl + CaI_2 \longrightarrow 2\,RCOI + CaCl_2$$

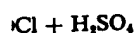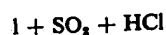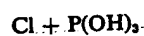$$RCOCl + HI \longrightarrow RCOI + HCl$$
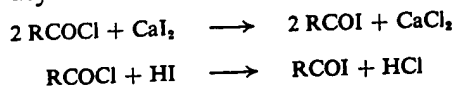
Similarly **acyl fluorides** are made from acyl chlorides and antimony fluoride or hydrogen fluoride.

carbon atoms are obtained
chain fatty acids have been
: antibiotic from *Bacillus*
tearic acid, from the fatty
tuberculosis, is 10-methyl-
paraffin from the Fischer-
5°–125° in the presence of
ier acids which served as a

of the hydroxyl group by a

$$\text{R}\overset{\overset{\textstyle O}{\|}}{—}\text{C}—\text{X}.$$

general formula R—C—X.
chloride, phosphorus penta-
nust be used to effect this
ides of phosphorous, phos-
Their reactions with organic
ins.

Cl + P(OH)₃

1 + POCl₃ + HCl

1 + SO₂ + HCl

Cl + H₂SO₄

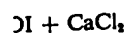phorus oxychloride also will

Cl + NaCl + NaPO₃

us pentachloride, three fifths
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Cl + 2 NaCl + NaPO₃

ther reagents in that the acyl
ed readily, the other products
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lic acids and inorganic acid
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ide or dry hydrogen iodide.

Cl + CaCl₂
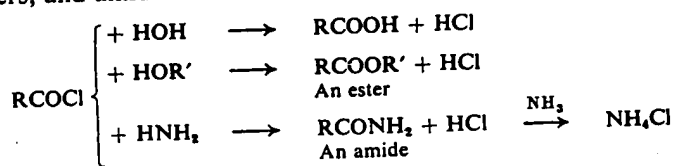
l + HCl

ides and antimony fluoride or

Nomenclature

Acyl halides are named by dropping the ending *ic acid* from the name of the corresponding acid and adding *yl halide*; for example CH₃COCl is acetyl chloride or ethanoyl chloride, and (CH₃)₂CHCOBr is *i*-butyryl bromide or 2-methylpropanoyl bromide. If common names are used for acyl halides having more than five carbon atoms in the chain, the ending is *oyl*. Thus lauric acid gives rise to lauroyl chloride. Where confusion may arise between common names systematic names should be used.

Physical Properties

Since the acyl halides do not contain hydrogen united to oxygen, no proton bonding can occur; hence they have normal boiling points. For example, acetic acid with a molecular weight of 60 boils at 118°, but acetyl chloride of molecular weight 78.5 boils at 51°. This value is between the boiling points of pentane (mol. wt. 72, b.p. 36°) and hexane (mol. wt. 86, b.p. 69°). Acyl halides are insoluble in water, the covalently-bound halogen atom having the effect of about two or three methylene groups in reducing the water solubility due to the carbonyl group. The acyl halides have a sharp odor and an irritating action on the mucous membranes.
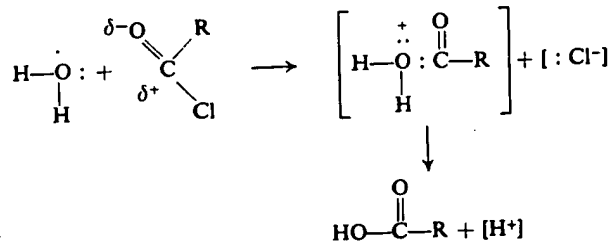
Reactions

1. **With Water, Alcohols, and Ammonia.** The acyl halides may be considered as mixed anhydrides of a carboxylic acid and hydrogen halide and as such react like anhydrides in general with water, alcohols, and ammonia, giving acids, esters, and amides.

$$\text{RCOCl}\begin{cases} + \text{HOH} \longrightarrow \text{RCOOH} + \text{HCl} \\ + \text{HOR}' \longrightarrow \text{RCOOR}' + \text{HCl} \quad \text{An ester} \\ + \text{HNH}_2 \longrightarrow \text{RCONH}_2 + \text{HCl} \overset{\text{NH}_3}{\longrightarrow} \text{NH}_4\text{Cl} \quad \text{An amide} \end{cases}$$

In the last reaction two moles of ammonia are required, since its rate of reaction with hydrogen chloride is greater than its rate of reaction with acyl chloride.

The greater ease of hydrolysis, alcoholysis, and ammonolysis of acyl halides when compared with alkyl halides may be ascribed to the inductive effect of the doubly bound oxygen atom (p. 153), which causes a lower electron density on the carbonyl carbon atom. The rate of reaction with electron-donating reagents is faster for acyl halides than for alkyl halides, even though the same inductive effect decreases the tendency of the chlorine to leave as a chloride ion.

$$\text{H—}\overset{\overset{\textstyle H}{\|}}{\text{O}}: + \overset{\delta^-O}{\underset{\delta^+\diagdown Cl}{\diagup}}\text{C}\diagdown\text{R} \longrightarrow \left[\text{H—}\overset{+}{\underset{H}{\text{O}}}:\text{C}\overset{\overset{\textstyle O}{\|}}{—}\text{R}\right] + [:Cl^-]$$

$$\downarrow$$

$$\text{HO—}\overset{\overset{\textstyle O}{\|}}{\text{C}}—\text{R} + [\text{H}^+]$$

The inductive effect of the oxygen also accounts for the greater ease of substitution of the α hydrogen by halogen, since the positive charge on the carbonyl carbon atom facilitates the loss of a proton from the α carbon atom (Sec. 3 below).
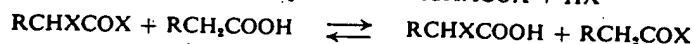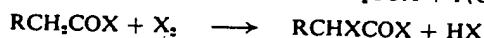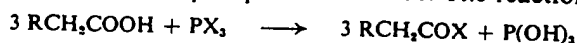
2. With Salts of Carboxylic Acids. Acyl halides react with metallic salts of organic acids to give *carboxylic acid anhydrides*.

$$RCOCl + NaO\overset{O}{\overset{\|}{C}}-R' \longrightarrow R\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}R' + NaCl$$
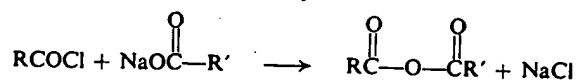
3. With Halogen. Acyl halides halogenate more readily than hydrocarbons and free acids. Moreover only an α hydrogen atom, that is, one on the first carbon atom adjoining the carbonyl group, is replaced readily.

$$RCH_2COX + X_2 \longrightarrow RCHXCOX + HX$$
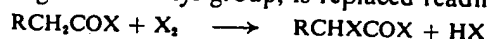
In actual practice free acids are used, the halogenation being carried out in the presence of a small amount of phosphorus trihalide. The reactions then are

$$3 RCH_2COOH + PX_3 \longrightarrow 3 RCH_2COX + P(OH)_3$$

$$RCH_2COX + X_2 \longrightarrow RCHXCOX + HX$$

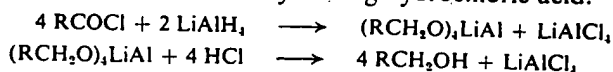$$RCHXCOX + RCH_2COOH \rightleftharpoons RCHXCOOH + RCH_2COX$$

Because of the last reaction a small amount of acid halide is sufficient to permit the direct halogenation of a large amount of acid. This procedure for making halogen acids is known as the *Hell-Volhard-Zelinsky reaction.*

4. Reduction. (*a*) CATALYTIC REDUCTION TO ALDEHYDES (*Rosenmund reduction*). Acyl chlorides can be reduced catalytically to aldehydes using a palladium catalyst. The catalyst usually is partially poisoned by the addition of sulfur compounds which renders it inactive for the catalysis of the further reduction of aldehydes to alcohols.

$$RCOCl + H_2 \overset{Pd}{\longrightarrow} RCHO + HCl$$
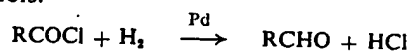
(*b*) LITHIUM ALUMINUM HYDRIDE REDUCTION TO ALCOHOLS. When an ether solution of lithium aluminum hydride is added to an acyl halide, reduction to the alcohol takes place. The product is the lithium aluminum salt of the alcohol, from which the alcohol is liberated by adding hydrochloric acid.
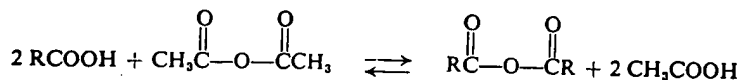
$$4 RCOCl + 2 LiAlH_4 \longrightarrow (RCH_2O)_4LiAl + LiAlCl_4$$

$$(RCH_2O)_4LiAl + 4 HCl \longrightarrow 4 RCH_2OH + LiAlCl_4$$

ACID ANHYDRIDES

Preparation

Two general methods for the preparation of acid anhydrides may be used, the first of which, from an acid halide and a salt, clearly defines the structure of carboxylic acid anhydrides.

$$R\overset{O}{\overset{\|}{C}}Cl + Na^+{}^-O\overset{O}{\overset{\|}{C}}R' \longrightarrow R\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}R' + NaCl$$
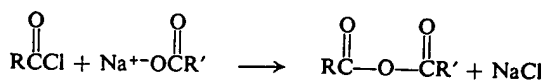
The second method depends on the fact that an equilibrium exists between carboxylic acids and acid anhydrides.

$$2 RCOOH + CH_3\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons R\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}R + 2 CH_3COOH$$

Left column (partial):

unds   Ch. 12

nd bases although Lowry[3] had
e Brønsted. It is of interest that
ated in 1923, the same year that
"the definition of an acid or a
vould be more general than the
considered the concept at least
more general one.

roton lacking a pair of electrons
i.

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$$\begin{bmatrix} \overset{+}{:}H \end{bmatrix}$$
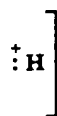
n any ion or molecule lacking a
ng an unshared pair of electrons.
aloride.

$$B : \overset{..}{\underset{..}{Cl}} \; Cl \; Cl^-$$
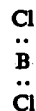
ied an acid as a substance which
l pair of electrons from another
uch as boron fluoride, aluminum
ne types of reaction, for example
i. 138), as can a proton.

nds often are called Lewis acids.
I that hydrogen chloride, sulfuric
bstances that from the beginning
e Lewis definition. The acid as
actically incapable of existence.
isidered as acids, are acids in the
ared pairs from other molecules,
ie cupric-ammonia complex ion.
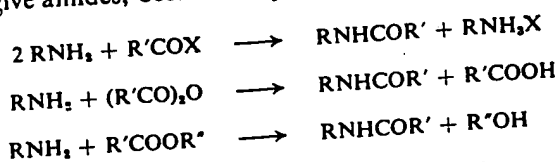
$$\begin{bmatrix} : NH_3 \end{bmatrix}^{++}$$
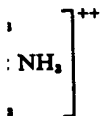
ke Institute of Copenhagen. His
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ysical chemistry at Cambridge
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: theory of valency, for his work
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Right column (main):

Instead of calling all types of compounds capable of accepting a pair of electrons acids, Sidgwick[5] in his book on valency published in 1927 called them electron-acceptors, thus leaving the term acid for those compounds capable of transferring a proton to a base. Perhaps a better term than electron-acceptor for reagents, such as boron trifluoride, aluminum chloride, stannic chloride, or zinc chloride, that behave like a proton, would be protonoid or protonoid reagent. This term would imply properties similar to those of a proton but would not group these compounds with the substances commonly called acids.

2. Alkylation. Since ammonia reacts with alkyl halides to give a mixture of primary, secondary, and tertiary amines, and quaternary ammonium salt (p. 229), amines also can react with alkyl halides to give secondary or tertiary amines, or quaternary salts.

3. Acylation. Acyl halides, acid anhydrides, and esters react with primary and secondary amines, just as they do with ammonia, to give amides. Tertiary amines do not give amides, because they do not contain a replaceable hydrogen atom.

$$2\,RNH_2 + R'COX \longrightarrow RNHCOR' + RNH_3X$$

$$RNH_2 + (R'CO)_2O \longrightarrow RNHCOR' + R'COOH$$

$$RNH_2 + R'COOR'' \longrightarrow RNHCOR' + R''OH$$

The reaction with acyl halides requires two moles of amine, only one of which can be acylated because the second mole combines with the hydrogen halide. Although an acid is formed in the second reaction, it is a weak acid, and the salt of a weak base and a weak acid dissociates sufficiently to produce the acylated amine when heated with an excess of anhydride. Hence all of the amine can be converted into amide by this procedure.

The products formed are known as *N-substituted amides*, the N referring to the nitrogen atom of the amide. Thus the reaction product of methylamine with acetic anhydride, $CH_3CONHCH_3$, is called N-methylacetamide. Secondary amines in the above reactions yield N,N-disubstituted amides. *i*-Butyryl chloride and diethylamine give N,N-diethyl-*i*-butyramide, $(CH_3)_2CHCON(C_2H_5)_2$.

An important application of the acylation reaction is the separation of tertiary amines from a mixture with primary and secondary amines. After acetylation with acetic anhydride, the unchanged tertiary amine may be separated from the higher boiling amides by distillation, or by extraction with dilute acid. The tertiary amine is basic and forms water-soluble salts whereas the amides are neutral. Similarly acylation can be used to distinguish tertiary amines from primary or secondary amines.

4. Isocyanide (Carbylamine) Test for Primary Amines. When a primary amine is heated with chloroform and a few drops of an alcoholic solution of sodium hydroxide, an *isocyanide* (*isonitrile* or *carbylamine*) is formed.

$$RNH_2 + CHCl_3 + 3\,NaOH \longrightarrow RNC + 3\,NaCl + 3\,H_2O$$
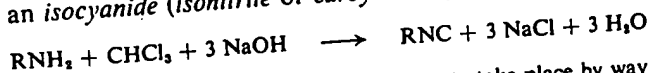
Reactions involving chloroform and strong alkali appear to take place by way of the highly reactive dichloromethylene radical (p. 175).

$$CHCl_3 + KOH \longrightarrow [:CCl_2] + KCl + H_2O$$
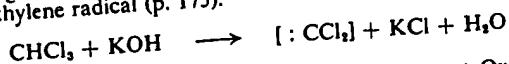
[5] Nevil Vincent Sidgwick (1873–1952), professor of chemistry at Oxford University. His writings did much to disseminate ideas arising from the application of physical methods to organic chemical problems.